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# Highly active, thermo-responsive polymeric catalytic system for reuse in aqueous and organic CuAAC reactions

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**Abstract**

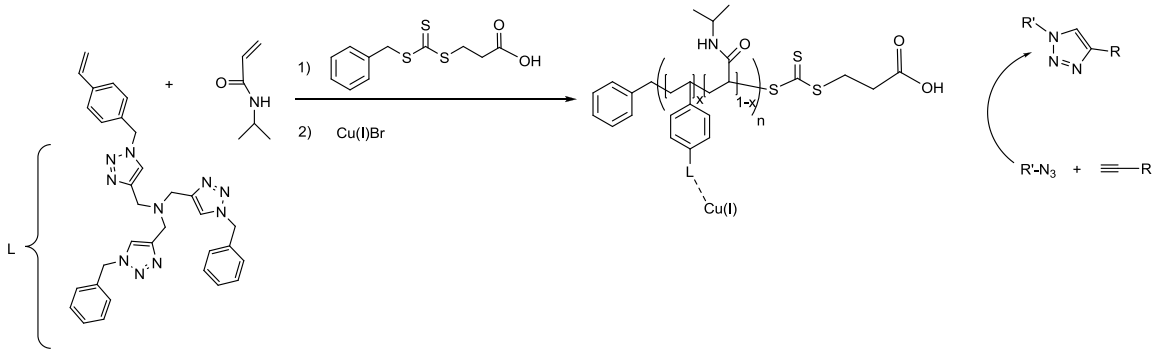
Tris-(benzyltriazolylmethyl)amine (TBTA) has been immobilized onto a styrenic monomer and subsequently copolymerized with N-isopropyl acrylamide (NIPAM) to afford catalytically active thermo-responsive copolymers for copper assisted click chemistry (CuAAC). P(TBTA-co-NIPAM) copolymers with narrow polydispersity indices (< 1.3) were synthesized with incorporation of between 2 to 10 ligand units per chain and tuneable molecular weight (28 to 148 kDa). A combination of $^{1}$H NMR spectroscopy, size exclusion chromatography (SEC) and elemental analysis (EA) confirmed the controlled synthesis of these polymers and allowed for quantification of the degree of TBTA-functionalized monomer incorporation. After loading with copper (I) bromide, this homogeneous catalyst system was added to a water/ethyl acetate two-phase system. Using this biphasic system aqueous click reactions could be performed at room temperature, while organic click chemistry could be performed above the cloud point temperature of the catalyst system. The polymer catalyst system could be regenerated via extraction by making use of its LCST-behaviour, and then reused for further CuAAC reactions. While a reduced catalytic activity is observed as a result of copper leaching in aqueous click reactions, the recycling experiments in the organic phase demonstrated that this copolymer supported system allows for efficient recycling and reuse.

## Introduction

Reversible Addition Fragmentation Chain Transfer (RAFT) polymerization has allowed the preparation of a wide range of stimuli-responsive polymers in a controlled fashion.[1-3] Among them the thermo-responsive polymer poly(N-isopropyl acrylamide) (PNIPAM) has gained a significant interest because aqueous solutions of PNIPAM exhibit a lower critical solution temperature transition (LCST) in the range of 28–32°C, depending on the aqueous solution composition.[4-6] When heated in water above this LCST-value, PNIPAM undergoes a reversible LCST-phase transition from a swollen hydrated state to a shrunken dehydrated state, losing about 90% of its *mass*. This very sharp transition (over ca. 5°C) in water, is attributed to the disruption of the hydrogen bonding of water molecules around the amide group of the side chain,[7-10] and has been used to control enzymatic activity[11], in affinity precipitation separation,[12] and as a protein recycling system.[13-14] Another growing area in which this property has been exploited is in supported catalysis.[15] Bergbreiter[16] synthesized a PNIPAM-bound-phosphine catalyst system that is soluble in aqueous or mixed aqueous/organic media and has a high activity in nucleophilic allylic substitution and in $sp$-$sp^3$ coupling reactions of aryl iodides with terminal alkynes. The catalyst can be recycled efficiently up to 10 times with an average reaction yield of 93%, by heating above PNIPAM's LCST in water, or by solvent precipitation. As regeneration of catalyst supported PNIPAM has been shown to be simple and quantitative, we opted to use this strategy for the preparation of an easily recoverable and reusable soluble polymer catalyst for CuAAC reactions.[15-16]

In our previous paper, the concept of such a soluble polymer catalyst system has been demonstrated for a polystyrene-based copper catalyst system.[17] After copolymerizing styrene with a ligand containing monomer TBTA-monomer, and subsequent copper(I) loading, this system was successfully (re)used (6 times) with a minimum loss of catalytic activity in organic media CuAAC reactions. However, some limitations have been realised for this supported system. In first instance, its hydrophobic nature makes its use in aqueous media impossible. Furthermore, after coupling of hydrophilic polymers, recovery of the catalyst system is problematic as both the catalyst system and reaction products precipitate in the same solvents. Therefore, we were interested in developing a broadly applicable catalyst system using this recently reported TBTA functional monomer.

Thus, we aimed at the development of an air-stable, highly reactive reusable polymer catalyst system for application in CuAAC reactions that works in both water and organic solvents and can be easily regenerated and reused by a simple extraction exploring its LCST-behaviour. For that reason, a styrene functionalized TBTA monomer was copolymerized with NIPAM using RAFT polymerization to afford a range of functional catalytic polymeric supports (Scheme 1). The influence of the incorporation of this TBTA-monomer on the LCST-behaviour of PNIPAM was investigated. Following loading of the polymer ligand with copper(I)bromide, the obtained polymer catalyst system was tested as a homogeneous catalyst system in both the water and ethyl acetate (EtOAc) phase of a two-phase $H_2O$/EtOAc system. The polymer catalyst system was regenerated via extraction above its LCST, which should allow for facile recycling and recovery of the supported catalyst.




**Scheme 1**. Depiction of the synthesis and (re) use of the P(TBTACu-co-NIPAM) catalyst system.

**Results and Discussion**

An overview of a series of random poly(TBTA-co-N-isopropyl acrylamide) (P(TBTA-co-NIPAM)) and corresponding reaction conditions is shown in Table 1. When using the optimal reaction conditions, e.g. 70°C in a 1:1 THF/DMF mixture for 20 hours and benzyl trithiocarbonate propionic acid (BTTCPA) as RAFT agent, a range of polymers containing varying degrees of TBTA incorporations (from 1% to 7%) and molecular weights (between 28 to 148 kDa) were obtained by selectively altering the theoretical TBTA monomer/styrene ratio (Entries 2, 3 and 6, Table 1) and reaction time (Entry 4, Table 1). The structures were analyzed by $^{1}$H NMR spectroscopy (Figure 1). Besides signals e and f ascribed to PNIPAM, characteristic broadened resonances originating from the TBTA monomers are visible at 5.5 (a and b) and 7.75 (c) ppm. Integration and comparison of these signals resulted in values for the TBTA/NIPAM ratio.

Molecular weights were determined by combination of $^{1}$H NMR spectroscopy and elemental analysis, as inaccurate molecular weight data are often observed for the SEC

analysis of amine containing polymers. This $M_{n,theo}$ was calculated as follows: (I) calculation of the amine (N) content via elemental analysis (via the N/S determination) (N = **Y**); (II) determination of the TBTA/NIPAM ratio (**X/Z**) by $^1$H NMR via comparison of the integrations of the TBTA signals (a, b and c) with e (Figure 1); (III) The equation **Y** = 10**X**+ **Z** (with **Z** = **X***ratio), provides the amount of incorporated TBTA (**X**) and subsequently the number-average molecular weight of the copolymer.

A kinetic run, performed for Entry 5 (Table 1), demonstrated that the reaction is well-controlled until ca. 30% conversion (right, Figure 2). This was evidenced by the linearity of the first order kinetic plot for both monomers and the linear increase of the $M_n$ versus the total conversion (taking the relative amount of each monomer in the reaction mixture into account (left, Figure 2)). The loss of control after 30% conversion can be ascribed to inefficient initiation and transfer reactions. This is evidenced by the SEC traces of the kinetic study, as depicted in Figure 2, for which the polymer traces shift to higher molecular weight with longer reaction times. Although no additional shoulders can be observed, the traces are quite broad, suggesting some minor contributions of side reactions. This broadening in molecular weight distribution is also visualized via $^1$H diffusion-ordered spectroscopy (DOSY, bottom left). The signals of the polymer chain as a function of diffusion coefficient are quite broad, indicating a less-defined polymer architecture. On the other hand, DOSY revealed that the TBTA monomer was indeed incorporated onto the PNIPAM backbone, as both the PNIPAM and the TBTA monomer possess the same diffusion coefficient.

To insure a better control over the polymerization and subsequent lower PDI-values, different reaction parameters, e.g. temperature, time and solvent were adjusted but even

despite many attempts to improve the polymerization, no increase in its control was observed.

**Table 1.** Reaction conditions and results for the synthesis of P(TBTA-co-NIPAM).

| Entry | TBTA-monomer (equiv.) | NIPAM (equiv.) | $M_{n,GPC}$ (kDa) | $M_{n,theo}$ [a)] (kDa) | PDI | TBTA/ NIPAM[b)] | Total TBTA-units[a)] | $T_{CP}$ (°C) |
|---|---|---|---|---|---|---|---|---|
| **PNIPAM** | - | 300 | 13.7 | 28.2 | 1.3 | - | - | 32 |
| **1** | 10 | 300 | 9.2 | nd | 1.5 | 1/27 | nd | nd |
| **2** | 10 | 300 | 10.6 | nd | 1.5 | 1/14 | nd | nd |
| **3** | 5 | 300 | 11.6 | 39.5 | 1.4 | 1/45 | 7 to 8 | 43 |
| **4** | 5 | 500 | 9.4 | 28.2 | 1.7 | 1/45 | 5 to 6 | 38 |
| **5** | 10 | 1000 | 16.9 | 63.2 | 1.6 | 1/75 | 7 to 8 | 36 |
| **6** | 10 | 1500 | 17.8 | 147.9 | 1.6 | 1/126 | 10 | 37 |
| **7** | 10 | 75 | 19.7 | nd | 1.5 | 1/55 | nd | nd |
| **8** | 2 | 30 | nd | nd | nd | 1/10 | 2 | 52 |

The reactions were performed for 20 hours at 70°C; Solvent 1:1 THF/DMF mixture; initiator: azobisisobutyronitrile (AIBN) (0.5 equiv.); RAFT-agent: BTTCPA (1 equiv.); [a)] determined via combination of EA and $^1$H NMR analysis; [b)] determined via $^1$H NMR analysis; [c)] reaction time of 30 hours; nd = not determined.

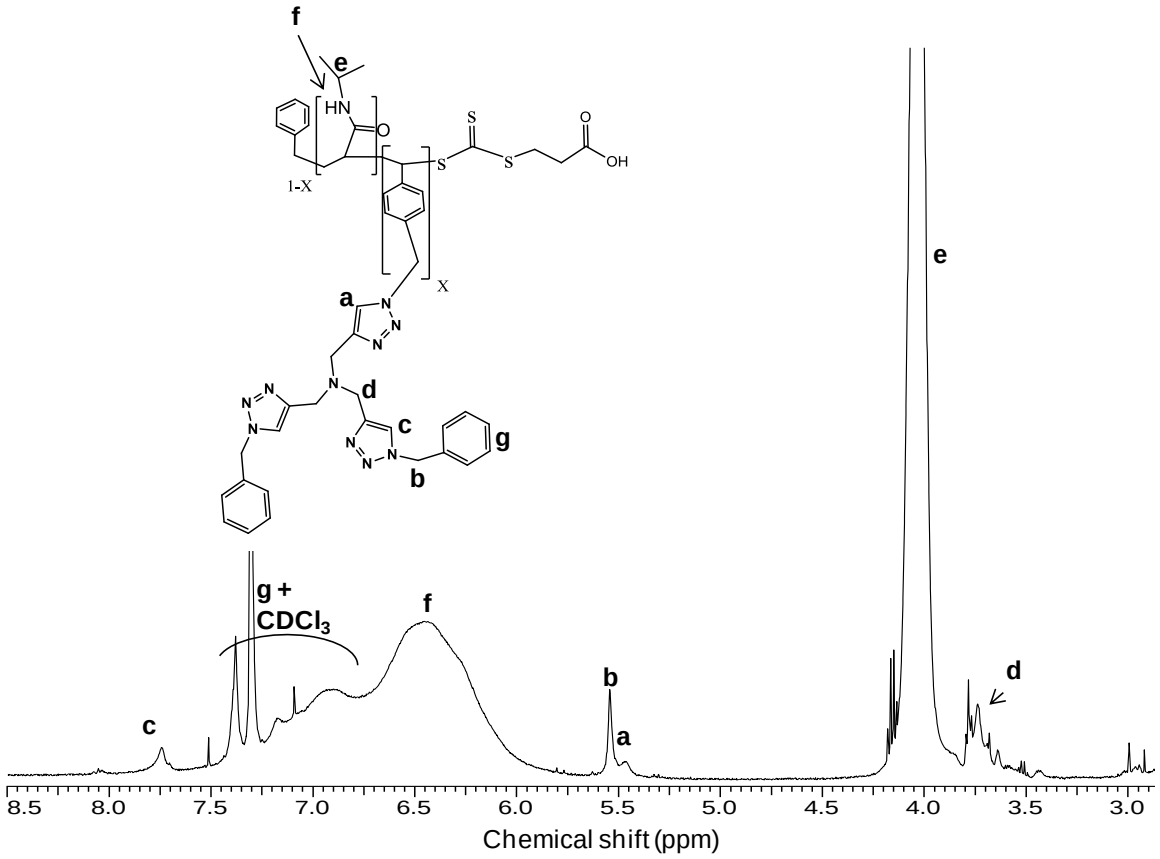



**Figure 1.** $^{1}$H NMR spectrum of P(TBTA-co-NIPAM) copolymer (500 MHz, $CDCl_3$).

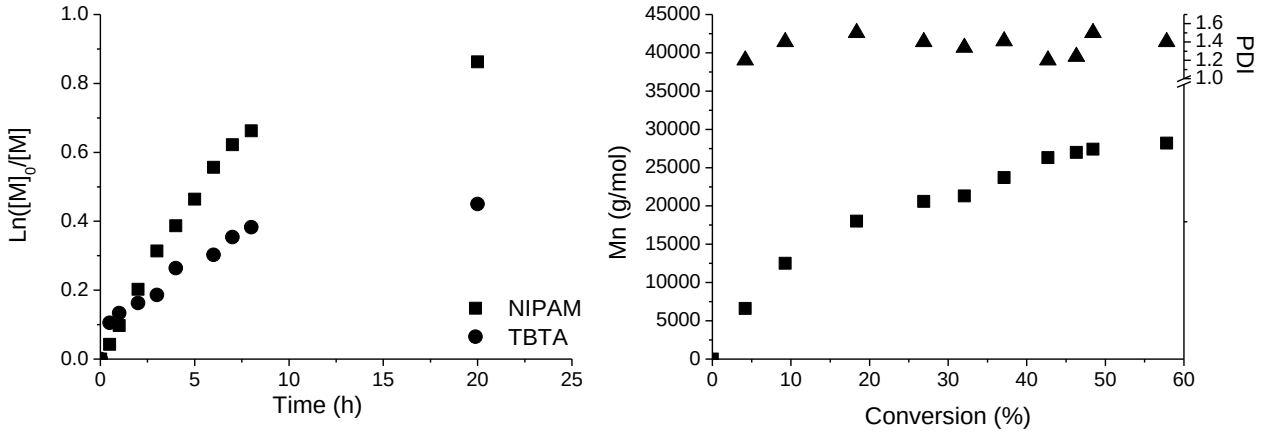



**Figure 2.** Kinetics of the synthesis of P(TBTA-co-NIPAM). First order kinetics (left) and evolution of $M_n$(■) and PDI (▲) with conversion; SEC DMA, (right) (calibrated with PMMA standards) (Entry 5, Table 1).

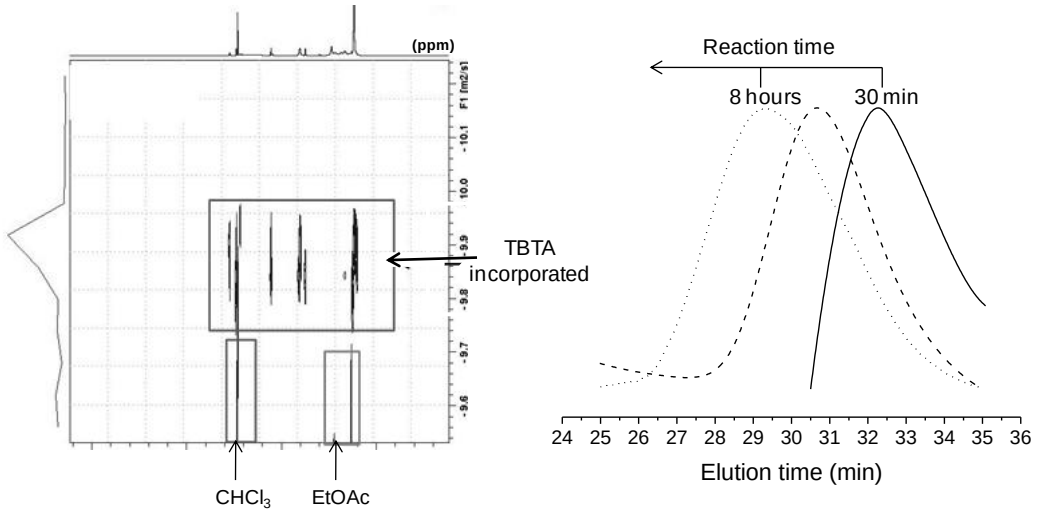



**Figure 3**. DOSY NMR of P(TBTA- co-NIPAM (left) (500 MHz, $CDCl_3$) and SEC of the kinetic study (right).

The phase transition behaviour and the cloud point temperature ($T_{CP}$) of the copolymers were studied as a function of TBTA and NIPAM content using UV-VIS measurements. The $T_{CP}$ values in water of the different catalyst systems having varying TBTA/NIPAM ratios are shown in Table 1. It has to be mentioned that all measurements were performed for the same concentration (0.005M). In first instance, the influence of the total amount of incorporated TBTA onto the PNIPAM was investigated. Therefore, UV-VIS measurements were performed on two polymers with similar TBTA/NIPAM ratios but different amount of incorporated TBTA. As could be seen from Table 1 (Entries 3 and 4), an increase in $T_{CP}$ was observed with increasing incorporation of TBTA. These results are consistent with literature examples, wherein a similar increase was observed by implanting other hydrophilic, amine containing monomers onto the PNIPAM backbone.[18] As expected, an increase in TBTA/NIPAM ratio resulted in higher $T_{CP}$-values (Entries 3 and 5, Table 1). As seen from Table 1 and Figure 3, a lower TBTA/ratio results in a $T_{CP}$ value that is close to

that of linear PNIPAM. Furthermore, the influence of copper on the $T_{CP}$ of P(TBTA-co-NIPAM) has been investigated. Surprisingly, the $T_{CP}$ of the copper loaded P(TBTACu-co-NIPAM) is higher than that of P(TBTA-co-NIPAM) (43°C and 35°C, respectively). The opposite effect was expected as copper is complexing the amines, making them less available for hydrogen bond formation (Figure 4, right). However, a plausible explanation is the solubilization of copper at higher temperatures, which resulted in a higher catalyst system's $T_{CP}$ value.

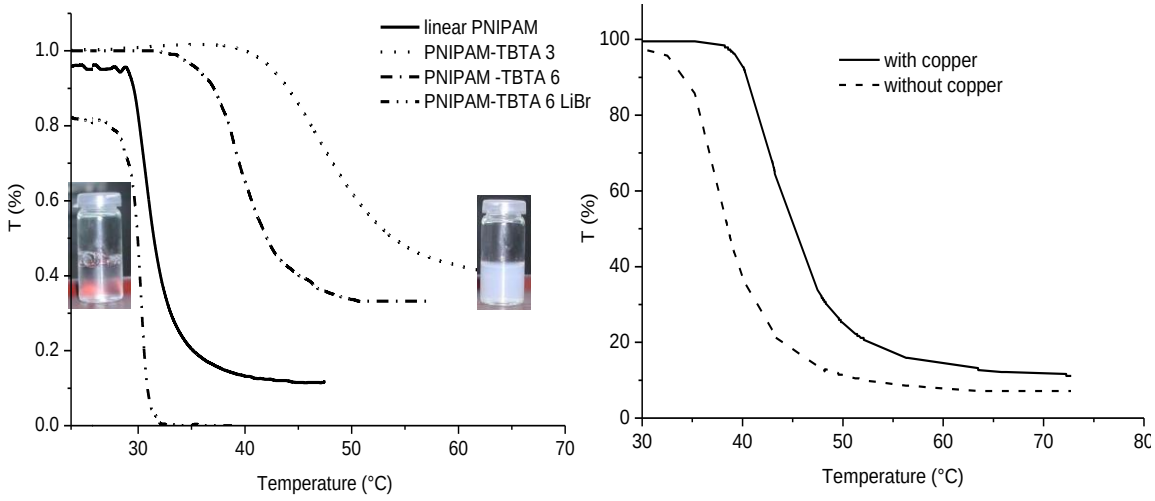



**Figure 4.** Determination of the cloud point (PNIPAM and copolymers of entry 3 and 6) by measuring the transmission of UV light through an aqueous solution containing the polymer ligand (1 mg/mL), as a function of temperature (left). Difference in $T_{CP}$ for the polymer ligand P(TBTA-co-NIPAM) (entry 6) before and after copper loading (right).

As for this work, $T_{CP}$-values similar to those of PNIPAM are preferable, the influence of a lithium bromide (LiBr) salt on the $T_{CP}$ was investigated. As expected, hydrogen bonds are broken in the presence of the $Li^+$ salt, leading to a lowering in $T_{CP}$, as evidenced for Entry 6 in Figure 4 (left).

**P(TBTA-co-NIPAM) as reusable catalyst system**

The polymer ligand P(TBTA-co-NIPAM) was, similar to the polystyrene catalyst system in earlier studies, loaded with copper(I)bromide in degassed THF by stirring for 24 hours. The loading densities of Cu(I) onto these polymers were determined using atomic absorption spectroscopy (AAS), and were consistent with the theoretical determined value (e.g. 4400 ppm for Entry 6, Table 1). Subsequently, P(TBTACu-co-NIPAM) copper-loaded copolymers were tested as homogeneous reusable catalyst systems for CuAAC in both the organic and aqueous phase of a biphasic system by making use of its LCST-behaviour. Aqueous and organic CuAAC were performed below and above the $T_{CP}$, respectively. However, finding the selective organic solvent was cumbersome as the solvent should fulfil several characteristics. Firstly, it must be immiscible with water and secondly it must solubilize P(TBTACu-co-NIPAM) above the $T_{CP}$. However, the affinity of the solvent towards the polymer catalyst should be limited below $T_{CP}$, such that after cooling the two-phase system to room temperature, P(TBTACu-co-NIPAM) returns to the aqueous phase. Finally it must have a relatively high boiling point as the system needs be heated above the $T_{CP}$ value when utilized in the organic click reaction.

From the wide range of tested solvents, only ethyl acetate seemed to fulfil these conditions. The EtOAc/$H_2O$ two-phase system was in first instance used for organic click reactions above the $T_{CP}$. Figure 5 gives a schematic overview of the organic CuAAC and recovery of P(TBTACu-co-NIPAM) in the two-phase system. In a first step, the copper-loaded polymer system (0.005 M) was dissolved in water (with 5% LiBr) at room temperature. After addition of an EtOAc phase, containing the clickable compounds (a), the system was heated

above the $T_{CP}$. As a result of the thermo-responsive character of PNIPAM, the catalyst system migrates to the organic phase (b), starting the CuAAC reaction (c). This phase transfer is visible to the eye. The yellowish coloured P(TBTACu-co-NIPAM) is in the lower aqueous phase at room temperature (**1**, Figure 5). When heating the system to 40°C, the organic phase becomes yellow (**2**, Figure 5), which is an indication for the successful phase transition. After 24 hours, the two-phase system was cooled down to 0°C (d), resulting in the extraction of the catalyst system into the aqueous phase. By a simple decantation, the EtOAc phase, containing the reaction product was separated from the aqueous phase (e). The cycle could be repeated by adding a new organic phase, containing the clickable compounds. Recyclability of the catalyst system (Entry 6 in Table 1) was examined by performing the CuAAC reaction between benzyl azide (BzAz) and phenylacetylene (PhAc) several times with the same catalyst system. When using following reaction conditions, P(TBTACu-co-NIPAM) (0.1 equiv. to the azide, 0.005 M) , PhAc (1.1 equiv.) and BzAz (1 equiv.) at 45°C in a water/EtOAc two-phase system for 24 hours, the catalyst system could be recycled at least up to 5 times, without large changes in activity (Figure 6). Using the fresh catalyst system, a conversion of 95% was achieved within 24 hours. Furthermore, a negligible decrease in activity was observed with successive reuse (still 89% conversion after the $5^{th}$ reuse). One reason for this decrease is some minimum loss of the catalyst system during the extraction procedure. This is evidenced by the presence of the catalyst system in the slightly yellowish reaction product, as seen from AAS. The copper amounts in the reaction product varied between 13 and 32 ppm. Moreover, the presence of a sulphur containing compound originating from the RAFT-group in the reaction products, as seen from elemental analysis, confirmed this observation.

To explore if the reactions could be performed in the presence of a lower amount of catalyst system, similar experiments were performed with 0.05, 0.01 and 0.005 equiv. of Cu(I) (Entry 6, Table 1). The experimental results for the experiments with 0.05 and 0.01 equiv. are very similar to those obtained for the previous discussed system (0.1 equiv.), as shown in Figure 6. Yields up to 88% were observed after the 5$^{th}$ reuse, showing the strength of this catalyst system at low catalyst concentrations. However, when performing the click reaction with 0.005 equiv. Cu(I), a decrease in catalytic activity was observed after the second use (from 95% to 67% yield). As this reaction was performed with a lower amount of catalyst, the loss of catalyst system during the work-up is believed to result in a more pronounced loss of catalytic activity.

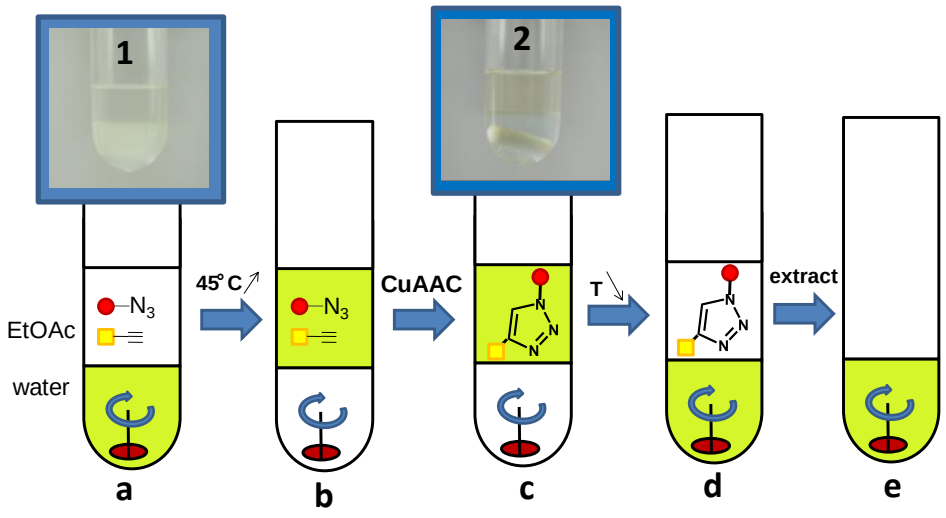



**Figure 5.** Schematic overview of the use (b+c) and recovery (d+e) of P(TBTACu-co-NIPAM) in a water/ethyl acetate two-phase system.

Besides clicking two low molecular weight compounds, a second set of click reactions explored the coupling of low molecular weight alkynes, e.g. phenylacetylene, onto an azide-terminated linear polymer, poly(isobornyl acrylate) PiBA-$N_3$ ($M_n$ = 15.000 g/mol) using 0.1 equiv. of the catalyst system. After separation of the catalyst system from the reaction product by a simple extraction below the catalyst system's $T_{CP}$, the endgroup functionalized polymer revealed a conversion of 82% after 24 hours as determined via $^1$H NMR, and a copper leaching of 12 ppm as determined via AAS. This incomplete click reaction was attributed to the bulkiness of the PiBA polymer, which limits the accessibility of the azide end-groups.

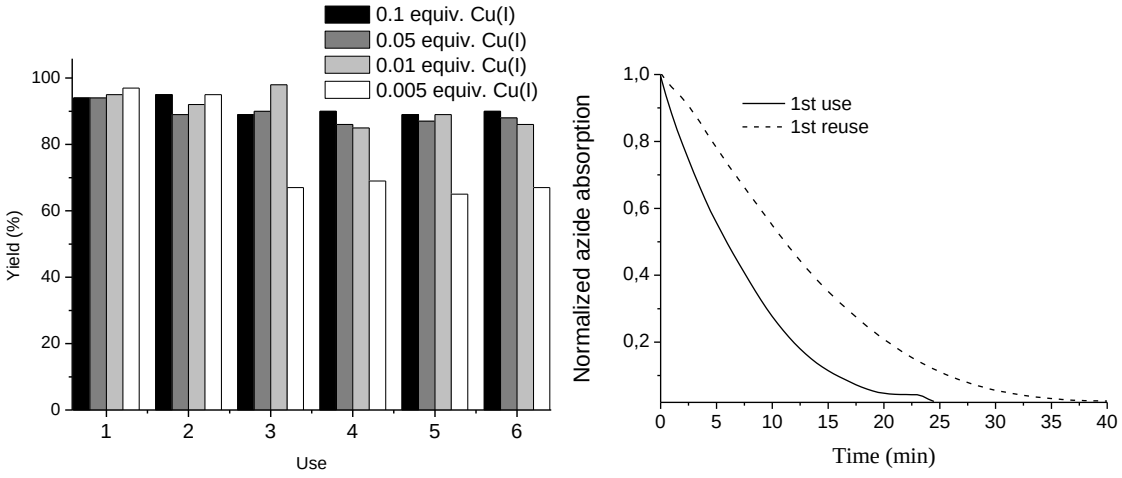



**Figure 6.** (left) Yields obtained for the CuAAC reaction between phenylacetylene and benzyl azide in EtOAc at 45°C by using different amounts of P(TBTACu-co-NIPAM) as a function of its reuse. (right) Testing the reusability of the P(TBTACu-co-NIPAM) for the homogeneous CuAAC reaction of 3-azidopropanol and propargyl alcohol in water at room temperature as a function of time.

Moreover, the system could be applied in aqueous click reactions by simply adding water soluble clickable compounds to the water phase of the two-phase system and performing click reaction at room temperature. In this case, the reaction product should be recoverable by heating the reaction mixture above the $T_{cp}$ of the catalytic system. In this project, the aqueous click reaction between propargyl alcohol and azido containing poly(ethylene oxide) (550 g/mol) was performed using Entry 6 (Table 1) at room temperature for 24 hours. Removal of the catalyst system occurred by heating the reaction mixture to 45°C and subsequent extraction of the EtOAc phase containing P(TBTACu-co-NIPAM). After regeneration of the catalyst system, recycling was performed by adding a new aqueous phase. From Figure 6 it can be concluded that a maximum yield of 98% (for 0.005 equiv. Cu(I)Br) was obtained after a reaction time of 24 hours. However with successive reuse, a larger decrease in catalytic activity was observed. This was also demonstrated by the kinetic study of the aqueous click reaction of propargyl alcohol and 3-azidopropanol. Figure 6 indeed shows a decrease of reactivity as a function of time (from 25 minutes for the $1^{st}$ use, to 40 minutes for the $2^{nd}$ use) as a result of a small loss of polymer catalyst. This was confirmed by the analysis of the end products for copper contamination. Considering that the initial copper loading was 4400 ppm, the leaching observed corresponds to 10 to 15 weight % of the original amount of copper on the polymer catalyst. From the latter results could be concluded that when the catalyst system remains too long in the aqueous phase (24 hours), copper leaches from the polymer catalyst. Therefore, when using this system to catalyze aqueous click, additional copper loading after every cycle is required to maintain its high activity.

**Table 2.** Yields obtained for the CuAAC reaction between propargyl alcohol and azido-PEO in water at room temperature using P(TBTACu-co-NIPAM) (Entry 6, Table 1) and copper determination in the clicked compound as determined by AAS.

| Use | Yield[1)] | Copper conc.[2)] (% of original amount Cu) |
|---|---|---|
| 1 | 98 | 460 |
| 2 | 95 | 680 |
| 3 | 96 | nd |

[1)] determined via $^1$H NMR analysis; [2)] determined via AAS; nd = not determined.

**Experimental:**

Sodium azide ($NaN_3$), phenylacetylene (98%, Aldrich), DMF, diethyl ether, LiBr (99,999%, Aldrich), $CuSO_4.5H_2O$ (98%, Aldrich), sodium ascorbate (> 99%, Aldrich), sodium bicarbonate (> 99%, Acros), ammonium chloride (> 99%, Acros), tert-BuOH, EtOAc, THF, dioxane and diethoxypropyne were used as received. 4-Chloromethyl styrene (90%, Aldrich) and styrene (99%, Aldrich) were distilled under reduced pressure. Azobisisobutyronitrile (AIBN, 98%, Aldrich) was recrystallized from MeOH (2 times) and stored at -4 $^oC$. Cu(I)Br (98%, Aldrich) was purified by stirring with acetic acid, washed with methanol, and finally dried under vacuum at 70 °C. Benzyl azide[19] and poly(ethylene oxide) containing two azide chain ends ($N_3$-PEO-$N_3$)[19], N,N-Bis[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]prop- 2-yn-1-amine[20] and benzyl trithiocarbonate propionic acid (BTTCPA)[21] were synthesized according to literature reports.

$^1$H NMR spectra were recorded in $CDCl_3$ at room temperature on a Bruker AM500 spectrometer at 500 MHz or on a Bruker Avance 300 at 300 MHz. Size Exclusion Chromatography (SEC) was performed on three in series placed polymer standards services SEC columns (1 x GRAM analytical 30 Å, 10 μm en 2 x GRAM Analytical 1000 Å, 10 μm) equipped with a waters 2414 refractive index detector(RI) with N,N'-dimethylacetamide (DMA) containing 0.42 mg/L lithium bromide, as an eluent at a flow rate of 1 mL/min). Poly(methyl methacrylate) standards were used for calibration. Molecular weight and polydispersity index were determined using the Empower software from Waters. Gas chromatography was performed on a GC8000 from CE instruments with a DB-5MS column (60m x 0.249 mm x 0.25 μm) from J&W scientific. Injections were performed with a CTC A2OOS autosampler. Detection was done with a FID detector. Injector and detector temperatures were kept constant at 250°C. The column was initially set at 50°C for 2 minutes, followed by a heating rate of 5°C/min until 260°C, and then held at this temperature for 8 minutes. At this temperature conversion was determined using decane as internal standard. Infrared spectra were obtained with ReactIR 4000 instrument (Mettler Toledo AutoChem React IRTM) using a silicone probe (SiComp, optical range 4400-650 $cm^{-1}$). For online measurements, the probe was introduced into a two-necked glass flask and spectra were recorded every 30 seconds for 3 hours. Elemental analyses (EA) were performed by Warwick Analytical Services and all measurements were performed in duplicate. Atomic absorption analyses (AAS) were performed with a VARIAN spextrAA-140. The samples were prepared as follows: samples were weighed into porcelain crucibles. They were pre-ashed in a muffle furnace at a temperature of 250°C and subsequently ashed during 3 hours at 450°C. The crucible was transferred to a hot plate, 5 mL of 6 M $HNO_3$ was added and the mixture was evaporated to a low volume. The

residue was dissolved in 5 mL of 3 M $HNO_3$, filtered (S&S, blue ribbon, Schleicher & Schuell, Dassel, Germany) and diluted to 50 mL.

*P(TBTA-co-NIPAM)*

A solution of NIPAM, TBTA-monomer, RAFT agent, AIBN and solvent was prepared ($[RAFT]_0$/[AIBN] is 1:0.5) and placed in a 10 mL flask. After six freeze–pump–thaw cycles, the solution was heated under stirring to 70 °C. After 20 hours, the reaction was quenched by placing the flask in an ice/water bath under air. The TBTA-containing PNIPAM was isolated by a two-fold precipitation into cold diethyl ether.

*$Cu^I$ loading*

In a 25 mL flame-dried two–necked round bottomed flask, TBTA-containing PNIPAM was dissolved in degassed THF, after which copper (I) bromide (1.05 equiv.) was added, under a nitrogen flow. The mixture was stirred overnight and subsequently precipitated into degassed diethyl ether. The greenish powder was dried under vacuum.

*(Re)usability tests*

*Organic CuAAC*

Cu complexed TBTA-containing PNIPAM was dissolved in water (2 mL). After addition of an EtOAc phase containing benzyl azide or PiBA-$N_3$ and phenylacetylene, the mixture was heated to 45°C to start the reaction. After 24 hours, the mixture was cooled down in the fridge after which the EtOAc phase, containing the clicked compounds, was extracted and solvent and excess of phenylacetylene was evaporated off. For the reuse, a new EtOAc phase containing clickable compounds was added.

*Aqueous CuAAC*

Cu complexed TBTA-containing PNIPAM was dissolved in the aqueous phase (2 mL), containing propargyl alcohol and azido containing poly(ethylene oxide) (550 g/mol) or 3-azidopropanol, of a two-phase $H_2$ O/EtOAc system. After 24 hours, the mixture was heated to 45°C after which the aqueous phase, containing the clicked compounds, was extracted and water and excess of phenyl alcohol was removed by freeze-drying. For the reuse, the EtOAc phase containing the catalyst system was added to an aqueous phase containing clickable compounds.

## Conclusion

In conclusion, thermo-responsive polymer ligands were synthesized and subsequently loaded with copper and applied as a reusable polymer catalyst system for click reactions in both the water and EtOAc phase of a two-phase system. First, the catalyst system was applied in the organic phase at 40°C, after which it was regenerated via an extraction into the aqueous phase by making use of its LCST-behaviour. For click reactions between small molecules, an almost quantitative yield was obtained within 24 hours, even after the $5^{th}$ reuse. On the contrary, when applying the same reaction conditions for end-group modification of polymers via CuAAC, only 82% conversion was obtained as a result of steric constraints. Finally, the catalyst system was tested for aqueous click reaction at room temperature, yielding a high click efficiency after 24 hours. However, due to copper leaching in the aqueous phase, the catalytic activity is decreasing. Further improvement of the reaction conditions would be necessary to minimize the copper leaching in these aqueous conditions.

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## Figure Legends

**Scheme 1**. Depiction of the synthesis and (re) use of the P(TBTACu-co-NIPAM) catalyst system.

**Figure 1.** $^{1}$H NMR spectrum of P(TBTA-co-NIPAM) copolymer (500 MHz, $CDCl_3$).

**Figure 2.** Kinetics of the synthesis of P(TBTA-co-NIPAM). First order kinetics (left) and evolution of $M_n$(■) and PDI (▲) with conversion; SEC DMA, (right) (calibrated with PMMA standards) (Entry 5, Table 1).

**Figure 3.** DOSY NMR of P(TBTA- co-NIPAM (left) (500 MHz, $CDCl_3$) and SEC of the kinetic study (right).

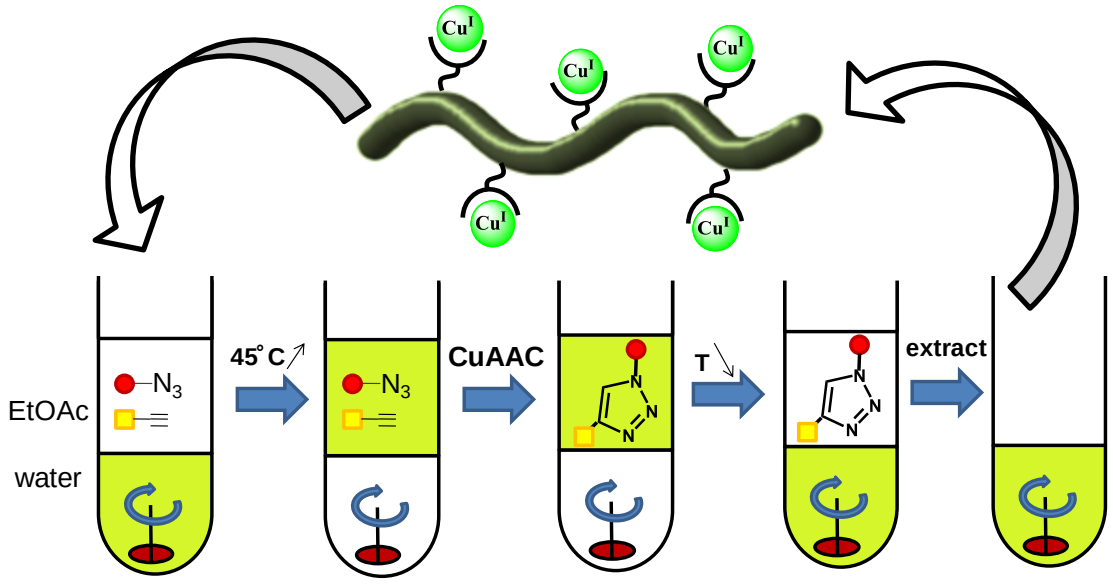
**Figure 4.** Determination of the cloud point (PNIPAM and copolymers of entry 3 and 6) by measuring the transmission of UV light through an aqueous solution containing the polymer ligand (1 mg/mL), as a function of temperature (left). Difference in $T_{CP}$ for the polymer ligand P(TBTA-co-NIPAM) (entry 6) before and after copper loading (right).

**Figure 5.** Schematic overview of the use (b+c) and recovery (d+e) of P(TBTACu-co-NIPAM) in a water/ethyl acetate two-phase system.

**Figure 6.** (left) Yields obtained for the CuAAC reaction between phenylacetylene and benzyl azide in EtOAc at 45°C by using different amounts of P(TBTACu-co-NIPAM) as a function of its reuse. (right) Testing the reusability of the P(TBTACu-co-NIPAM) for the

homogeneous CuAAC reaction of 3-azidopropanol and propargyl alcohol in water at room temperature as a function of time.

**Graphical Abstract**




Highly active and reusable polymeric catalysts were produced by RAFT polymerization of N-isopropyl acrylamide with a TBTA-containing monomer, followed by copper (I) loading. The copper-loaded thermo-responsive copolymers are excellent, recyclable catalysts for CuAAC reactions in both water and organic solvent. The polymer catalyst system was regenerated via extraction by making use of its LCST-behaviour.